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Conformational Preferences of *trans*-1,2- and *cis*-1,3-Cyclohexanedicarboxylic Acids in Water and Dimethyl Sulfoxide as a Function of the Ionization State As Determined from NMR Spectroscopy and Density Functional Theory Quantum Mechanical Calculations

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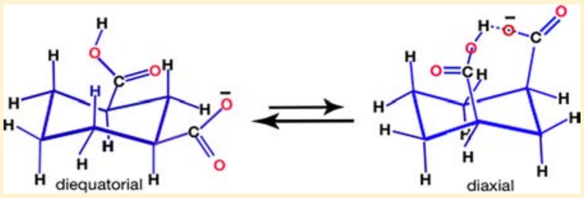
Supporting Information



ABSTRACT: The populations of diaxial (*aa*) and diequatorial (*ee*) conformers of *trans*-1,2- and *cis*-1,3-cyclohexanedicarboxylic acids (CDCAs; **1** and **2**, respectively) and their salts were determined in water and dimethyl sulfoxide (DMSO) solutions from vicinal proton−proton NMR *J* couplings ($^3J_{HH}$). Optimized geometries and free energies for these compounds were obtained at the M06-2X/cc-pVTZ(-f)++ level. Although carboxylic acid groups in cyclohexane rings are generally believed to be far more stable (~2 kcal/mol) in equatorial than axial positions, this investigation demonstrated that an *aa* conformation (normally assumed to be completely insignificant for these compounds) can be favored depending on the medium and ionization state: strong *ee* preferences (>90%) were observed in water and DMSO for both diacids and their salts, except for the dianion of **1** in DMSO, which was found to be substantially *aa* (~57%). The possibility of intramolecular hydrogen bonding (H-bonding) was also investigated; the ratios of the ionization constants (K_1/K_2) indicated an absence of intramolecular H-bonding because $K_1/K_2 \ll 10^4$ (a standard criterion for non-H-bonding in dicarboxylic acids) for both **1** and **2** in water and also for **2** in DMSO. For **1**, K_1/K_2 increased drastically in DMSO ($K_1/K_2 = 4 \times 10^6$), where $^3J_{HH}$ and the ratio $K_1/K_E = 10$, K_E being the acidity constant of the monomethyl ester of **1**, indicated the formation of an intramolecular H-bond for the monoanion in this solvent. An explanation for the observation of compact dianions in solution in terms of the generalized Born equation is also provided.

■ INTRODUCTION

Understanding how solvent properties and molecular interactions determine conformational preferences is useful for rationalizing organic reactions,[1] for the intelligent design of drugs[2] and molecular switches.[3] Six-membered rings are an important system for the study of conformational analysis.[4] Even so, conformational analysis data available in the literature for cyclohexanes with pairs of interacting substituents are relatively scarce,[5] compared to data available for monosubstituted rings. For *trans*-1,2- and *cis*-1,3-cyclohexanedicarboxylic acids (CDCAs; **1** and **2**, respectively; see Scheme 1), the method for assignment of the conformation by Corey[5] predicts the difference in free energy between diaxial (*aa*) and diequatorial (*ee*) conformers, $\Delta G = G_{aa} - G_{ee}$, to be about 3−4 kcal/mol. From the Boltzmann distribution, such a large ΔG would completely prevent the observation of sizable *aa* populations, and thus, the *aa* conformations are commonly believed to be insignificant for **1** and **2**. Investigation as to whether electrostatic repulsions (in the dianion of **1**) or intramolecular H-bonding (in the monoanion of **2**) can favor the *aa* isomer was of interest for us in connection with recent conformational studies of succinic acid in solution which have shown unexpected results, e.g., ~40−60% *gauche* preference for the dianion in D_2O, dimethyl sulfoxide (DMSO), and tetrahydrofuran (THF).[6]

On the basis of evidence from ^{13}C NMR satellites, Abraham and Hudson[7] concluded that, in water, **1** displayed *ee* preference and that there were few or no conformational differences between the diacid and dianion; nevertheless, no attempt was reported to determine the conformer populations or to investigate solvent effects on the conformational preferences. Compound **2** has been studied in the solid state by X-ray diffraction, where it was found in an *ee* conformation with intermolecular H-bonding between the carboxylic acid groups.[8]

In the present work, the changes in conformational preferences were investigated as a function of the solvent and ionization state for **1** and **2**. Ionization constants and density functional theory (DFT) quantum mechanical calculation data

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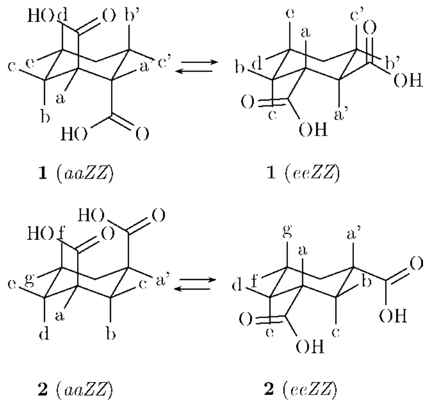
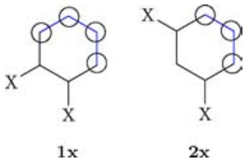
Scheme 1. Structures and Labeling of Protons for 1 and 2



1 (*aaZZ*) **1** (*eeZZ*)

2 (*aaZZ*) **2** (*eeZZ*)

Scheme 2. CCH_2CH_2C Fragments for 1,2-Disubstituted Cyclohexanes



aided in the interpretation of such preferences; theoretical conformer populations were also computed and compared to the experimental results. Parallels were drawn between **1** and succinic acid. In addition, procedures were derived to simplify the process of measuring couplings in large spin systems by iterative simulations, to analyze complex spectra on the basis of ^{13}C satellites, and to determine λ values for the Altona equation[9] from substituents in six-membered rings.

RESULTS AND DISCUSSION

Determination of Conformer Populations from NMR Proton–Proton Couplings. Assuming that the proton exchange is fast on the NMR time scale, a particular coupling, J_{exptl}, for a diacid is given by

$$J_{\text{exptl}} = F_{H_2A}J_{H_2A} + F_{HA^-}J_{HA^-} + F_{A^{2-}}J_{A^{2-}} \qquad (1)$$

where F_j and J_j denote the fraction and coupling, respectively, of species j. Furthermore, if the conformer population consists only of *aa* and *ee* and the rate of interconversion is also fast on the NMR time scale, then

$$J_j = x_{ee}^{j}J_{ee}^{j} + (1 - x_{ee}^{j})J_{aa}^{j} \qquad (2)$$

where x_{ee}^{j} is the *ee* fraction of the j species and J_{ee}^{j} and J_{aa}^{j} are the coupling constants for the j species in the *ee* and *aa* conformations, respectively. Hence, if F_j, J_{ee}^{j}, and J_{aa}^{j} are known, only three independent measurements of J_{exptl} are required to solve for x_{ee}^{j} (i.e., with three measurements at different pH values, we can construct a system of linear equations from eqs 1 and 2 and solve for x_{ee} for each of the ionization species). We focus now on how to obtain accurate estimates of F_j, J_{ee}^{j}, and J_{aa}^{j}.

In aqueous solution, F_j was calculated from pK values reported in the literature[10] using eqs 3–5. These equations can be derived readily from the definitions of K_1 and K_2 by noting that $F_{H_2A} + F_{HA^-} + F_{A^{2-}} = 1$. In DMSO solution, F_j was determined from the integrals of the signals of the counterion (tetrabutylammonium) and the chemical shifts of the CDCAs in the ^{1}H NMR spectra.

$$F_{H_2A} = \frac{[H^+]^2}{K_1K_2 + K_1[H^+] + [H^+]^2} \qquad (3)$$

$$F_{HA^-} = \frac{K_1[H^+]}{K_1K_2 + K_1[H^+] + [H^+]^2} \qquad (4)$$

$$F_{A^{2-}} = \frac{K_1K_2}{K_1K_2 + K_1[H^+] + [H^+]^2} \qquad (5)$$

The magnitudes of J_{ee}^{j} and J_{aa}^{j} in CCH_2CH_2C fragments (indicated in Scheme 2) were estimated from

$$^3J_{HH} = 11.16\cos^2\phi - 1.28\cos\phi + 0.77 \qquad (6)$$

Equation 6 is a Karplus-type equation parametrized to describe $^3J_{HH}$ in CCH_2CH_2C fragments of six-membered rings and was shown to give better results than the Altona equation.[11]

Estimates of $^3J_{HH}$ for the remaining protons of the CDCAs employed the empirical λ values from the Altona equation,[9]

$$^3J_{HH} = 14.63\cos^2\phi - 0.78\cos\phi + 0.60 + \sum_i \lambda_i[0.34 - 2.31\cos^2(\zeta_i\phi + 18.4|\lambda_i|)] \qquad (7)$$

The parameter ζ_i can take values of +1 or −1 depending on the relative orientation of substituent i.[9] Dihedral angles, φ, for eqs 6 and 7 were extracted from geometries optimized at the M06-2X/cc-pVTZ(-f)++ level. The λ values utilized are shown in Table 1 and were obtained from the literature or through Altona's procedure, except for the CH_2 group of the ring, λ_r, because the Altona procedure requires that the group of unknown λ be attached to a substituted ethane (CH_3CH_2X or CH_3CHXY). However, x_{ee}^{j} could be established for **1** and **2** from the CCH_2CH_2C couplings. With x_{ee}, it was possible to solve for J_{ee}^{j} and J_{aa}^{j} and then make these couplings congruent with eq 7; λ_r was calculated by finding the expression $\lambda_r = f(\lambda_r)$ and applying the fixed point method.[12]

Table 1. Empirical λ Values for the Altona Equation (Eq 7) Utilized in This Work

	λ			
	H(−CH_2−)	COOH	COO^-	CH_2(ring)
water	0.00[a]	0.39[a]	0.41[a]	0.81[a]
DMSO	0.00[a]	0.41[b]	0.20[b]	0.81[b]

[a] Reference 9. [b] This work.

Determination of Coupling Constants from NMR Spectra by Iterative Simulations. For samples in D_2O, proton–proton J couplings were measured by iterative simulations of the ^{1}H NMR spectra using full-line-shape analysis in the gNMR software.[13] The process of analyzing the spectra by this means was simplified with the aid of eqs 1 and 2 using the user-defined variables and relations options in gNMR, where the couplings were defined in terms of the known values of F_j, J_{ee}^{j}, and J_{aa}^{j} and an unknown variable, x_{ee}^{j}. By defining these relationships, the number of independent variables was greatly reduced and the least-squares optimization of the parameters was simplified. This method is general and can be applied whenever eqs 1 and 2 hold.

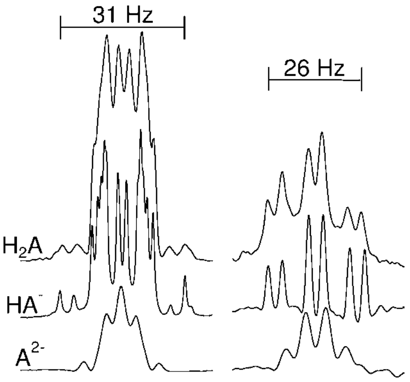


Figure 1. Experimental ^1H NMR spectra (left) and ^{13}C satellites (right) for proton a (α-proton) of **1** and its ionization species in DMSO-d_6.

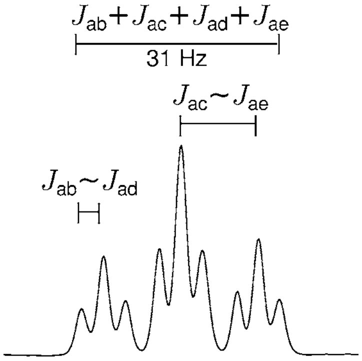


Figure 2. Experimental NMR spectrum of proton a (α-proton) of **2** in DMSO-d_6 showing a triplet of triplets pattern that allows for direct estimation of coupling constants.

In DMSO, however, interference from overlapping signals of the counterion precluded the use of full-line-shape analysis. In this case, the most convenient method to calculate x^j_{ee} was to analyze the spectral widths, W, of specific signals. For **1**, simulations showed a triplet of doublets with $W = J_{aa'} + J_{ab} + J_{ac}$ for the ^{13}C satellite signal of proton a (see Scheme 1 for the labeling). The computed satellite spectra were in agreement with the experimental spectra of **1** and its ionization species (see Figure 1), and thus, x^j_{ee} could be determined from the spectral widths of this signal. For **2**, x^j_{ee} was unambiguously established from spectral widths of proton a, $W_a = J_{ab} + J_{ac} + J_{ad} + J_{ae}$ (Figure 2), and proton c, $W_c = J_{ac} + J_{bc} + J_{ca'}$ (Figure 3). The values for J_{bc} were obtained from the ^1H spectra. The relationships between spectral widths and J couplings were corroborated with spectral simulations. A comparison of a representative sample of estimated and experimental couplings and spectral widths appears in Table 2.

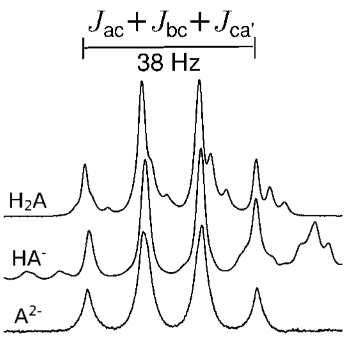


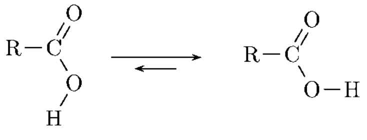
Figure 3. NMR spectra of proton c of **2** and its ionization species in DMSO-d_6. The spectrum of the dianion shown was obtained from an NOESY 1D experiment (proton b was irradiated) because of overlapping with other signals. The value of J_{bc} is negative, but for convenience, we refer here to its absolute value.

Table 2. Comparison of Estimated and Experimental Couplings and Spectral Widths[a]

compd	species	solvent	param	theoretical[b]		exptl[b]
				aa	*ee*	
1	H_2A	D_2O	$J_{ee'}$	2.4	13.1	13.01
1	H_2A	DMSO	W_a	8.1	27.1	25.9
1	HA^-	D_2O	$J_{ee'}$	2.9	13.0	12.9
1	HA^-	DMSO	W_a	8.1	27.6	27.2
1	HA^{2-}	D_2O	$J_{ee'}$	2.6	13.1	12.6
1	A^{2-}	DMSO	W_a	8.3	28.3	16.9
2	H_2A	D_2O	J_{eg}	2.6	13.1	13.2
2	H_2A	DMSO	W_c	~17.5[c]	37.6	37.6
2	HA^-	D_2O	J_{eg}	2.7	13.2	13.2
2	HA^-	DMSO	W_c	~17.5[c]	37.8	36.9
2	A^{2-}	D_2O	J_{eg}	2.7	13.2	13.2
2	A^{2-}	DMSO	W_c	~17.5[c]	37.6	37.6

[a] Only a subset of representative couplings are shown (see the Supporting Information). [b] Hertz units. [c] Different estimates of W_c^{aa} do not affect the calculated x^j_{ee} because $W_c^{\mathrm{exptl}} \approx W_c^{ee}$.

Conformational Preferences of *trans*-1,2-CDCA: Observation of Intramolecular H-Bonding and the *aa* Conformation. Figure 4 shows the experimental and theoretical x^j_{ee} for **1** at 25 °C and compares these results to those reported for succinic acid. Considering the accuracy of the level of theory and the assumptions made by the solvation models utilized,[14] the agreement between experiment and computation is remarkably good. For the monoanion of **1** in water, the SM6 solvation model[15] gave results in closer agreement with experiment than the Poisson−Boltzmann model, which predicted the *aa* isomer to be dominant (see Table 3). Similarly, MP2/aug-cc-pVTZ calculations gave better results than M06-2X for the dianion in water. The *E* and *Z* isomers of the carboxylic acids were both considered; however, the Z acids were calculated to be much more stable than their *E* counterparts, except for the intramolecular H-bonded monoanion (*eeE*), in agreement with previous investigations of succinic acid.[16,17] The optimized geometries for these isomers are illustrated in Figure 5, and the calculated relative free energies are given in Table 3. Here, in addition to the *ee* and *aa* labels, the *E* and *Z* letters are being used to denote the conformation of the donating carboxylic protons relative to the carbonyl in each conformer (**3**). Note that the *E* conformation is required for intramolecular H-bonding.



3 (*E*) **3** (*Z*)

A large *ee* preference ($x_{ee} \approx 1$) was observed for **1** and its salts in solution; however, the $^3J_{HH}$ data indicated $x_{aa} \approx 0.57$ for the dianion in DMSO. Solution-phase calculations predicted $x_{aa} \approx 0.12$ for the dianion in DMSO. Although the computed x_{aa}

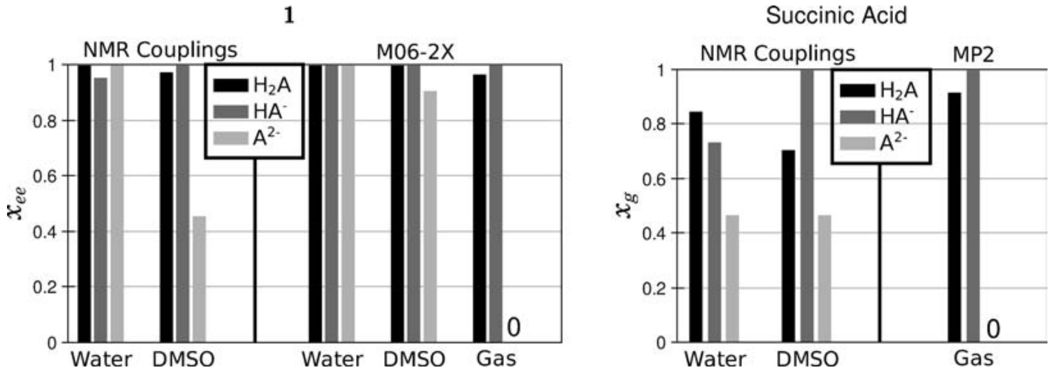
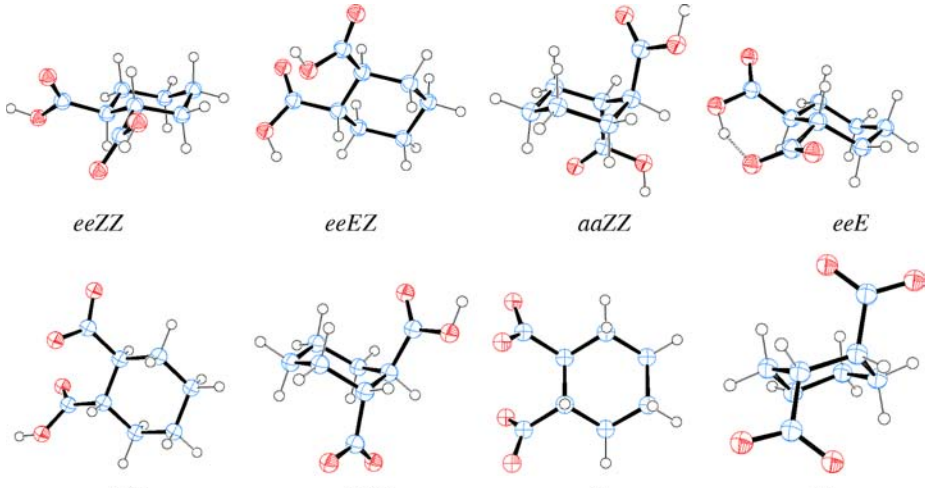


Figure 4. Experimental ($^3J_{HH}$) and theoretical (M06-2X/cc-pVTZ(-f)++) *ee* fraction (x_{ee}) for **1** (left) in water, DMSO, and the gas phase at 25 °C. Theoretical populations were calculated using the Boltzmann distribution. The energies of the mono- and dianions of **1** in water were refined by the SM6 solvation model (M06-2X/6-31+G**) and single-point energy calculation at MP2/aug-cc-pVTZ, respectively. These results are compared to the *gauche* fraction (x_g) of succinic acid obtained from data available in the literature.[6,16,17]



eeZZ *eeEZ* *aaZZ* *eeE*

eeZ *aaZ* *ee* *aa*

Figure 5. ORTEP[18] structures (from M06-2X/cc-pVTZ(-f)++-optimized geometries in DMSO) for a representative sample of conformers of **1** and its mono- and dianions. The molecular geometries computed for these conformers change only slightly among the gas phase, water, and DMSO.

Table 3. Computed M06-2X/cc-pVTZ(-f)++ Free Energies at 25 °C in the Gas Phase, Water, and DMSO for the Most Stable Conformers of 1 and Its Ionization Species

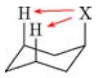
		relative free energy[a]		
species	conformer	gas	H_2O	DMSO
H_2A	*eeZZ*	0.00	0.00	0.00
	aaZZ	1.63	2.41	2.46
	eeEZ	6.74	2.94	3.44
	aaEZ	7.18	5.21	6.17
HA^-	*eeE*	0.00	0.00	0.00
	aaZ	19.30	−1.31	6.04
	eeZ	14.79	2.47	3.69
	aaE	17.17	2.60	8.28
A^{2-}	*ee*	0.00	0.00	0.00
	aa	−14.12	0.55	1.16

[a]Kilocalories per mole relative to the corresponding *ee* conformations.

differs significantly from the experimental value, translating conformer populations into energy differences at 298 K, the error is approximately 1.3 kcal/mol (the chemical accuracy achieved by quantum chemistry composite methods is generally considered to be about 1 kcal/mol).[14] The observed chemical shifts were in agreement with $x_{aa} \approx 0.57$; for completely *ee* conformations, the equatorial protons appeared at low field relative to the axial ones and were clearly distinguishable from such, while averaged chemical shift values were observed for the dianion of **1**. Electrostatic repulsions between the vicinal carboxylate groups could be responsible for the 57% *aa* preference for the dianion, but that has not been established.

The finding of a large x_{aa} is particularly notable as it demonstrates the influence of solvent on conformational preferences and because carboxylate groups are commonly believed to be much more stable (~2 kcal/mol for each axial group) in equatorial than in axial positions, even when vicinal to each other.[5] In fact, we are not aware of any reported *trans*-1,2-disubstituted cyclohexane that shows such a large *aa* preference without additional substituents.

Parallels were found between **1** and succinic acid. For both diacids, the COOH groups show a *gauche* preference; the larger extent of this preference in **1** can be attributed to 1,3-*syn*-diaxial interactions (**4**) not present in succinic acid. An analogous



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remark can be made about the mono- and dianions in water. In addition, the monoanion of succinic acid appears to form an intramolecular H-bond in DMSO but not in water,[6,16,19] and **1** displayed a similar behavior. The 100% *ee* preference of the monoanion of **1** allows for the possibility of an intramolecular H-bond. As shown in Table 4, for both **1** and succinic acid, $K_1/K_2 < 10^4$ in water and $K_1/K_2 > 10^4$ in DMSO. For dicarboxylic acids, extensive thermodynamic studies indicate that intramolecular H-bonding may be important only when $K_1/K_2 > 10^4$.[20] Apparently, the low efficiency of DMSO to solvate anions, as compared to water, allows for the formation of intramolecular H-bonds; water is both a H-bond donor and a H-bond acceptor, but DMSO is only an acceptor, and thus, it is limited in its ability to solvate anions by intermolecular H-bonding.

Table 4. Acidity Constants of Succinic Acid (SA), 1, and 2 in Water and DMSO[a]

	In Water		
acid	pK_1	pK_2	K_1/K_2
SA	4.20[c]	5.55[c]	22
1	4.18[b]	5.93[b]	56
2	4.10[b]	5.46[b]	23

	In DMSO				
acid	pK_1	pK_2	K_1/K_2	pK_E	K_1/K_E
SA	9.5[c]	16.7[c]	1.6×10^7	11.6[d]	126
1	10.5[d]	17.1[d]	4×10^6	11.5[d]	10
2	11.6[d]	14.4[d]	630	11.9[d]	2

[a] The acidity constants of the monomethyl esters of these diacids in DMSO, pK_E, are also shown. The statistical ratios are $K_1/K_2 = 4$ and $K_1/K_E = 2$. Intramolecular H-bonding may be important only when $K_1/K_2 > 10^4$ and $K_1/K_E > 2$. [b] Reference 10. [c] Reference 30. [d] This work.

However, a large K_1/K_2 does not necessarily imply intramolecular H-bonding in the monoanion of a dicarboxylic acid; destabilization of the dianion might lead to large values of K_1/K_2, as occurs in (±)-2,3-di-*tert*-butylsuccinic acid.[21] Thus, comparisons were made between the values of K_1 for the diacids in DMSO and the acidity constants of their monomethyl esters, K_E. These values are shown in Table 4. The statistical ratio is $K_1/K_E = 2$, and $K_1/K_E > 2$ is indicative of stabilization in the monoanion of the diacid by intramolecular H-bonding.[22] The fact that the values of K_1/K_E for succinic acid and **1** are significantly larger than 2 (126 and 10, respectively) provides evidence for the intramolecular H-bonding in their monoanions in DMSO.

Further evidence of intramolecular H-bonding in the monoanion of **1** in DMSO was afforded by the chemical shifts of the acidic protons and the DFT quantum mechanical calculations: for the diacid, a sharp signal at 12 ppm was observed. For the monoanion this resonance became a broad peak at about 14.9 ppm. This signal could be more clearly observed in THF solution, where a behavior similar to that observed in DMSO is expected, at −80 °C at about 17.5 ppm (the signal became sharper, and thus observable, with a decrease in temperature; see Figure 6). Such a downfield shift is associated with protons that become less shielded when the O−H bond is extended to form an H-bond.[23] DFT optimizations for diacid **1** in DMSO gave a structure that was not H-bonded with an O−H distance of 0.97 Å (*eeEZ* in Figure 5). Similar calculations on the monoanion showed an asymmetric H-bond (the O−O distance was less than the sum of the van der Waals radii) with distances of 1.04 Å for the O−H bond and 1.43 Å for the O···H bond and an O−H···O angle of 166° (*eeE* in Figure 5). The finding of an asymmetric H-bond is in agreement with the studies by Perrin,[24] which suggest that symmetric H-bonds in dicarboxylic species are extremely rare in solution. Additionally, the *eeE* conformer was predicted to be about 3.7 kcal/mol (see Table 3) more stable than its *eeZ* counterpart in DMSO.

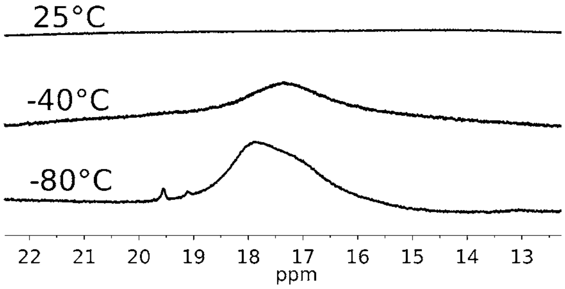


Figure 6. NMR signal for the acidic proton of the monoanion of **1** as observed at 25, −40, and −80 °C in THF.

Differences between the monoanion of **1** and monosuccinate were also noted. In DMSO, K_1/K_2 and K_1/K_E for succinic acid are, respectively, about 4 and 13 times greater than for **1** (Table 4). This observation indicates that H-bonding in monosuccinate might be more favorable than in the monoanion of **1**, possibly because in the latter the geometry is unfavorably restricted by the ring. The DFT calculations indicated that, for the *eeE* isomer of the monoanion of **1**, the dihedral angle between the carbonyl carbons is about 61°. For monosuccinate, this angle has been calculated to be nearly 80° to achieve the optimal geometry for the H-bond,[17] and the dipolar couplings of this monoanion in liquid crystal solution are consistent with 74(±4)°.[25]

The COO^- groups of the dianions of **1** and succinic acid in the gas phase and DMSO show strikingly similar *gauche* preferences (see Figure 4); each is about 0% in the gas phase (theoretical) and 43% in DMSO (experimental). The *gauche* preference of the COO^- groups is much lower in the gas phase than in solution, suggesting that a very significant stabilization results from bringing like-charged anionic groups together in solvent media. It has been suggested[6] that a possible rationalization for this observation could be provided by the Born equation,[26]

$$G_s = -\frac{1}{8\pi\varepsilon_0}\left(1 - \frac{1}{\varepsilon_r}\right)\sum_i^n \frac{q_i^2}{\alpha_i} \tag{8}$$

where G_s is the free energy required for transferring an ion from a vacuum to a medium of dielectric constant ε_r and α_i denotes the Born radius of species *i*. Thus, if we consider the *anti* conformation of disuccinate to consist of two separate charges, then $G_s \propto -2n(-1)^2$ for this conformer. If the *gauche* conformations are approximated as a single doubly charged species, then $G_s \propto -n(-2)^2$ for the *gauche* form, and hence, the stabilization is greater than for the *anti* conformer. However, eq 8 does not give the total free energy due to solvent−solute electrostatic polarization, G_{pol}. Taking into account the effect of the dielectric medium on the pairwise interactions of charged particles results in the generalized Born equation,[27]

$$G_{\mathrm{pol}} = -\frac{1}{8\pi\varepsilon_0}\left(1-\frac{1}{\varepsilon_{\mathrm{r}}}\right)\sum_i^n\sum_j^n \frac{q_iq_j}{f_{\mathrm{GB}}} \tag{9}$$

where $f_{\mathrm{GB}} = (r_{ij}^2 + \alpha_{ij}e^{-D})^{1/2}$, $\alpha_{ij} = (\alpha_i\alpha_j)^{1/2}$, and $D = r_{ij}^2/(2\alpha_{ij})^2$. The total electrostatic energy in solutions is given by eq 9 plus Coulomb's law in vacuo. Because f_{GB} is about 10 times more sensitive to small changes in r_{ij} than α_{ij},[27] we focus on the effect of r_{ij} on G_{pol}. As $r_{ij} \to 0$ (i.e., superimposed charges), $\partial G_{\mathrm{pol}}/\partial r_{ij}$ approaches zero, and this point corresponds to a minimum of G_{pol} with respect to r_{ij} whenever q_i and q_j have equal signs. Thus, polarization of the solvent by the solute stabilizes bringing like charges close together in dielectric media. Note also that when $r_{ij} = 0$, eq 8 is equal to eq 9, and that G_{pol} decreases with increasing ε_{r}. This observation might well be related to the increased preference of polar conformers in solvents of high dielectric constant.[28,29]

The computed solvation energies shown in Table 5 indicate that solvation tends to favor *ee* conformers, which were also calculated to be more polar than their *aa* counterparts. Also, solvation appears to stabilize *E* acids more than *Z* acids; an exception occurs for the *eeE* conformer, because its intramolecular H-bond reduces the interaction with the solvent, as compared to an isomer without intramolecular H-bonding. Solvation energies for anions are much larger than for neutral species because of the stronger polarization of the solvent by the solute, as the Born equation suggests.

Table 5. Solvation Energies for the Most Stable Conformers of 1 and Its Ionization Species Calculated at the M06-2X/cc-pVTZ(-f)++ Level Using the Poisson−Boltzmann Solvation Model To Mimic Solvent Effects

		solvation energy[a]	
species	conformer	water	DMSO
H_2A	*eeZZ*	−14.6	−16.6
	aaZZ	−13.5	−15.5
	eeEZ	−18.9	−23.7
	aaEZ	−16.8	−21.7
HA^-	*eeE*	−62.3	−68.9
	aaZ	−78.0	−74.7
	eeZ	−79.2	−76.8
	aaE	−77.2	−74.7
A^{2-}	*ee*	−221.7	−212.1
	aa	−207.9	−197.6

[a] Kilocalories per mole.

It is worth noting that the Born stabilization competes with repulsions arising from Coulomb's law, and thus, the overall effect may be difficult to predict. However, in general, the Born effect should make conformers bearing like charges close together more stable in dielectric media as compared to the gas phase.

Conformational Preferences of *cis*-1,3-CDCA: Strong *ee* Predilections. Figure 7 shows the experimental and theoretical x_{ee}^j for **2** at 25 °C. The optimized structures for the lowest energy conformers are depicted in Figure 8, and the calculated relative free energies are given in Table 6. The $^3J_{\mathrm{HH}}$ data indicated $x_{ee} \approx 1$ for **2**, and no important conformational changes with ionization were observed in solution. Strong *syn*-1,3-diaxial repulsions between the carboxylic groups are likely to be influential in determining the observed *ee* preferences, although solvation also appears to favor *ee* isomers (see Table 7). For the dianion, the optimization of an *aa* conformer at the M06-2X/cc-pVTZ(-f)++ level resulted in a twist-boat (*tb*) conformation, suggesting that steric and electrostatic repulsions between the *syn*-1,3-diaxial carboxylate groups can account for about 5.5 kcal/mol, which is approximately the energy difference between the cyclohexane chair and twist-boat conformations.[31] This energy difference is in very good agreement with the calculated relative free energies shown in Table 6.

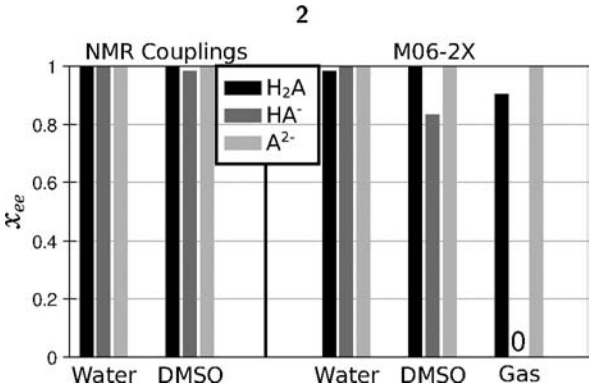
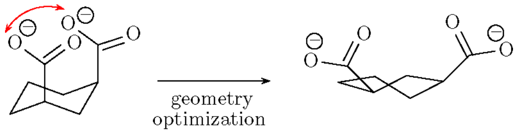


Figure 7. Experimental ($^3J_{\mathrm{HH}}$) and theoretical (M06-2X/cc-pVTZ(-f)++) *ee* fraction (x_{ee}) for **2** in water, DMSO, and the gas phase at 25 °C. Theoretical populations were calculated using the Boltzmann distributions. The energy of the monoanion in DMSO was refined by a single-point energy calculation at the MP2/aug-cc-pVTZ level.

Table 6. Computed M06-2X/cc-pVTZ(-f)++ Free Energies at 25 °C in the Gas Phase, Water, and DMSO for the Most Stable Conformers of 2 and Its Ionization Species

		relative free energy[a]		
species	conformer	gas	H_2O	DMSO
H_2A	*eeZZ*	0.00	0.00	0.00
	aaZZ	1.17	1.92	3.09
HA^-	*aaE*	0.00	0.00	0.00
	eeZ	11.14	−2.76	3.94
	aaZ	–	3.61	−0.02
A^{2-}	*ee*	0.00	0.00	0.00
	tb[b]	5.40	5.98	5.39

[a] Kilocalories per mole. [b] Optimization of *aa* gave a twist-boat (*tb*).



2 (*aa*) **2** (*tb*)

For both water and DMSO, the K_1/K_2 ratios (see Table 4) were less than 10^4 and similar in magnitude to those reported for diacids unable to form intramolecular H-bonds, such as fumaric acid ($K_1/K_2 = 200$ in DMSO).[30] Furthermore, the observed K_1/K_{E} in DMSO was $K_1/K_{\mathrm{E}} = 2$, which corresponds to the statistical ratio. $K_1/K_2 < 10^4$ and $K_1/K_{\mathrm{E}} \approx 2$ were anticipated as the *ee* conformation does not allow for intramolecular H-bonding in **2**.

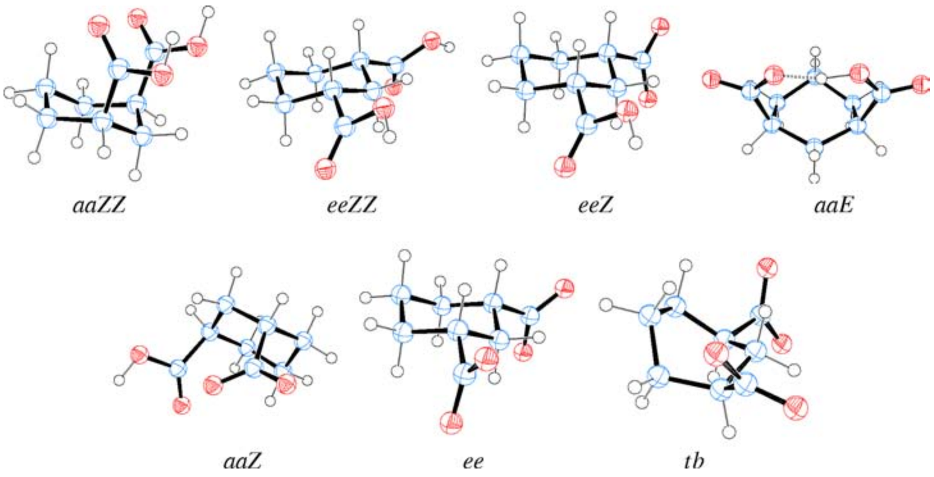


Figure 8. ORTEP[18] structures (from M06-2X/cc-pVTZ(-f)++-optimized geometries in DMSO) for a representative sample of conformers of **2** and its mono- and dianions. The molecular geometries computed for these conformers change only slightly among the gas phase, water, and DMSO.

Table 7. Solvation Energies for the Most Stable Conformers of 2 and Its Ionization Species Calculated at the M06-2X/cc-pVTZ(-f)++ Level Using the Poisson−Boltzmann Solvation Model To Mirror Solvent Effects

		solvation energy[a]	
species	conformer	water	DMSO
H_2A	*eeZZ*	−15.8	−18.4
	aaZZ	−14.2	−15.8
HA^-	*aaE*	−66.1	−64.0
	eeZ	−81.6	−76.5
A^{2-}	*ee*	−204.4	−196.6
	tb[b]	−203.8	−196.0

[a] Kilocalories per mole. [b] Optimization of *aa* gave a twist-boat (*tb*).

The M06-2X calculations provided insight into the lack of intramolecular H-bonding in the monoanion of **2** by suggesting that the geometry of the ring differs from an ideal cyclohexane chair (see *aaE* in Figure 8), because of the proximity of the carboxyl groups. To form an intramolecular H-bond, the dihedral angles ϕ_{ab}, ϕ_{ac}, ϕ_{ad}, and ϕ_{ae} (i.e., dihedral angles between the protons as labeled in **2**; see Scheme 1) are expected to change to about 79°, 35°, 70°, and 46°, respectively. These changes may in turn lead to torsional and angle strain. None of the alternative conformations computed in this work (*aaZ* and *eeZ*) were predicted to have such large deviations from the ideal 60° or 180° angles.

Interestingly, the calculations predicted a complete *aa* conformation with an intramolecular H-bond for the monoanion in the gas phase; in fact, no *aa* structure could be optimized in the gas phase without the intramolecular H-bond. Calculations for solutions showed that both *aa* structures, with (*aaE*) and without (*aaZ*) an intramolecular H-bond, are local energy minima. However, *aaE* was estimated to be 3.5−4.0 kcal/mol (see Table 6) more stable than *aaZ*, suggesting that formation of this bond might be possible if the carboxylic groups can be forced into axial positions or a more flexible ring system than cyclohexane is used.

■ CONCLUSIONS

The conformer populations of **1** and **2**, as well as their mono- and dianions, in water and DMSO were determined from $^3J_{HH}$. Close to 100% *ee* preferences were observed in water and DMSO for both diacids and their salts, except for the dianion of **1** in DMSO, which was found to be about 57% *aa*; this finding is particularly important because carboxylic groups are commonly believed to be largely more favorable in equatorial, than in axial, positions. Conformer populations were also computed from M06-2X/cc-pVTZ(-f)++ calculations; the results were in rather good agreement with experimental observations. The K_1/K_2 ratios were not large enough to be consistent with intramolecular H-bonding ($K_1/K_2 \ll 10^4$) for both CDCAs in water and for **2** in DMSO. $K_1/K_2 = 4 \times 10^6$, $K_1/K_E = 10$, and the low-field chemical shift of the acidic proton (∼17 ppm) gave substantial evidence of an intramolecular H-bond in the monoanion of **1** in DMSO. The results of this work support the generality of the phenomena observed for succinic acid in solution, most importantly (1) intramolecular H-bonding between vicinal dicarboxylic monoanions is likely to occur in DMSO but not in water and (2) bringing like charges close together in dielectric media creates a degree of stabilization because of polarization of the solvent by the solute. Such observations might help develop a general scheme for the prediction of conformational preferences in solution.

■ EXPERIMENTAL SECTION

Preparation of Samples in D_2O and DMSO. All samples and NMR solvents were obtained from commercial sources and used without further purifications. The pH values of the various samples were measured using a Thermo Scientific Orion 3 pH meter and 98 series pH probe calibrated with standard buffer solutions. Samples of these diacids were also prepared in 99.9% DMSO-d_6. The monoanions were prepared by weighing 15−25 mg (0.09−0.15 mmol) of the diacid along with an excess (2 equiv) of tetrabutylammonium cyanide in a positive pressure glovebox and dissolving the mixture in DMSO-d_6. Excess base was required to achieve complete formation of the monoanions. No important changes in $^3J_{HH}$ were observed by adding 1 or 2 equiv of base in DMSO. Because cyanide is a weaker base than the dianions of these compounds in DMSO (pK = 12.9 for HCN),[32] a different procedure was necessary to synthesize the dianions in this solvent. The dianions were thus prepared by weighing 15−25 mg (0.09−0.15 mmol) of the diacid along with 2 equiv of tetrabutylammonium cyanide in a positive pressure glovebox and dissolving the mixture in methanol. The methanol was then evaporated using an air stream, the oily sample was dried at high vacuum overnight, and the desired tetrabutylammonium salt was dissolved in DMSO-d_6.

Synthesis of Monomethyl Esters of Diacids. The monomethyl esters of **1**, **2**, and succinic acid were obtained by methanolysis of the respective anhydrides. Succinic anhydride was acquired from commercial sources. The anhydrides of **1** and **2** were obtained by sublimation from a mixture of the diacid with 4 times its weight of P_2O_5 at 120° under high vacuum.

Measurement of Ionization Constants in DMSO. The method described by Choi[30] was employed to determine the relative strengths of the acids from mixtures of the salt of the acid of unknown pK and a reference acid of known pK. Benzoic acid (pK = 11.1) and phthalic acid monoanion (monophthalate; pK_2 = 16) were used as references.[30] Monophthalate was prepared from phthalic acid by a procedure similar to that used for the synthesis of the mono- and dianions of the CDCAs. Solutions of benzoic acid and monophthalate in DMSO-d_6 were mixed with equimolar amounts of the mono- and dianions of the CDCAs, respectively. NMR spectra of the mixtures were recorded; for the mixtures at equilibrium, it can be shown that, for the diacids,

$$(\delta_a - \delta_{HA}) + (\delta_a - \delta_{H_2A})\left(\frac{\delta_b - \delta_B}{\delta_{HB} - \delta_b}\right)\left(\frac{K_{HB}}{K_1}\right) + (\delta_a - \delta_A)\left(\frac{\delta_{HB} - \delta_b}{\delta_b - \delta_B}\right)\left(\frac{K_2}{K_{HB}}\right) = 0 \quad (10)$$

and, for the monomethyl esters,

$$(\delta_a - \delta_A)\left(\frac{K_E}{K_{HB}}\right)\left(\frac{\delta_{HB} - \delta_b}{\delta_b - \delta_B}\right) + (\delta_a - \delta_{HA}) = 0 \quad (11)$$

where δ_i is the chemical shift of species i. Here, HB and B represent the reference acid species and δ_a and δ_b denote the chemical shifts of the CDCA and the reference acid, respectively, in the equilibrium mixtures. The values for δ_{H2A}, δ_{HA}, δ_A, δ_{HB}, δ_B, and K_{HB} were obtained from the literature or from standard preparations so that K_1 and K_2 were the only unknowns in eq 10. Hence, for each diacid, two measurements of mixtures (monoanion and benzoic acid, and dianion and monophthalate) were sufficient to solve for K_1 and K_2. The chemical shifts from the ^{1}H and ^{13}C NMR spectra, referenced to DMSO taken as 2.500 and 39.520 ppm, respectively, were used to solve for K_1 and K_2.

Measurement of Spectra. NMR spectra were recorded with a Varian Inova 600 NMR spectrometer using default pulse sequences in the VnmrJ software. In some cases, the ^{13}C satellite signals overlapped with residual solvent peaks at 600 MHz, so spectra were also taken with a Varian MR 400 NMR spectrometer. Low-temperature experiments were performed on a Varian Inova 500 NMR spectrometer. Typical running conditions of the spectrometers were as follows: ^{1}H spectra, 16 scans, spectral width 9600 Hz (6400 Hz for 400 MHz), relaxation delay 1 and 4 s of acquisition time. For nuclear Overhauser enhancement spectroscopy (NOESY) 1D experiments, an NOE mixing time of 500 ms was used. Unless otherwise indicated, spectra were measured with the temperature regulated at 25 °C.

Theoretical Calculations. All DFT quantum mechanical calculations were carried out with the Jaguar version 7.5, release 207, software package from Schrödinger, Inc.[33] For solution-phase calculations, the Poisson−Boltzmann continuum model was used. The SM6[15] model implemented in Jaguar was also utilized. Fully unconstrained geometry optimizations of all stationary points were performed using M06-2X[34] with Dunning's[35] cc-pVTZ(-f)++ basis set. Free energies of the compounds were calculated by performing frequency calculations on the optimized structures using the same functional and basis sets. The frequencies were scaled by 0.9721.[34] For the dianion of **1**, single-point energies were also calculated at MP2/aug-cc-pVTZ for the gas phase with the M06-2X-optimized geometries using the Molpro quantum chemistry package.[36]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and simulated NMR spectra, the parameters used to compute the latter, and .xyz files of the optimized structures from the theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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